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REVIEW

From nature versus nurture, via nature and nurture, to gene × environment interaction in mental disorders

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Abstract It is now generally accepted that complex mental disorders are the results of interplay between genetic and environmental factors. This holds out the prospect that by studying G × E interplay we can explain individual variation in vulnerability and resilience to environmental hazards in the development of mental disorders. Furthermore studying G × E findings may give insights in neurobiological mechanisms of psychiatric disorder and so improve individualized treatment and potentially prevention. In this paper, we provide an overview of the state of field with regard to G × E in mental disorders. Strategies for G × E research are introduced. G × E findings from selected mental disorders with onset in childhood or adolescence are reviewed [such as depressive disorders, attention-deficit/hyperactivity disorder (ADHD), obesity, schizophrenia and substance use disorders]. Early seminal studies provided evidence for G × E in the pathogenesis of depression implicating 5-HTTLPR, and conduct problems implicating MAOA. Since then G × E effects have been seen across a wide range of mental disorders (e.g., ADHD, anxiety, schizophrenia, substance abuse disorder) implicating a wide range of measured genes and measured environments (e.g., pre-, peri- and postnatal influences of both a physical and a social nature). To date few of these G × E effects have been sufficiently replicated. Indeed meta-analyses have raised doubts about the robustness of even the most well studied findings. In future we need larger, sufficiently powered studies that include a detailed and sophisticated characterization of both phenotype and the environmental risk.

Keywords Gene–environment interaction · Depressive disorders · ADHD · Obesity · Schizophrenia · Substance use disorders

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Introduction

Recent progress in the development of powerful new techniques for locating and identifying human susceptibility genes and genetic variations contributing to common diseases has created new opportunities to advance our understanding of the etiology of mental disorders. Two approaches, linkage and association analyses, have been

applied to identify and study genetic effects across a number of mental disorders. These disorders include attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, mood disorders, substance use disorders, schizophrenia, eating disorders, obesity, and anxiety disorders. However, despite initial optimism, few susceptibility genes (i.e., predisposing sequence variations) have been replicated with some consistency. Even for replicated findings the effects are very small: taking all risk genotypes into account explains only a small fraction of the variation in the expression of a disorder.

There are several possible explanations for this. One is that gene–environment interactions (G × E) have so far been largely ignored in the design and analyses of genetic studies. This has hampered the detection of significant genetic effects operating in those exposed to one environment and not another [69]. This notion is supported by the growing body of evidence for the contribution of genetic effects in explaining individual variability in response to all kinds of environmental hazards [68, 82, 83]. Because of this type of work it is nowadays generally accepted that complex mental disorders require an understanding of the interplay between genetic and environmental factors. This G × E hypothesis is neurobiologically plausible and is supported by a growing body of evidence (e.g., there are formal genetic studies in its favor [51]). However, some researchers remain skeptical and call for more robust replication of initial results [70]. Clearly much more work is needed to establish (1) the conditions under which G × E occur; and (2) the mechanisms that drive the G × E effects. Why do some genetic variants have effects only in the presence of a particular environmental exposure and/or vice versa [64]. The article starts with an overview of the impact as well as the limitations of G × E studies. In general, this is followed by more detailed information about G × E research findings in some selected mental disorders with onset in childhood or adolescence.

The importance of gene–environment interplay in the etiology of mental disorders

G × E provides a potential explanation of the individual differences in responses to environmental influences. G × E occurs when the effect of exposure to an environmental pathogen on a person's health is conditional on the genotype [19]. For example, children exposed to an environment stressor known to increase risk for a certain psychiatric disorder (e.g., high family adversity) are at a higher risk for that disorder if they carry particular gene variants which renders them more susceptible to that stressor (see Fig. 1).

Alternatively children carrying a genotype known to increase susceptibility for a specific mental disorder may only develop that disorder if they are exposed to specific environmental risk factors (see Fig. 2).

According to these models on the one hand, differences in individual genetic make-up are responsible for the differences between individuals with regard to resilience or vulnerability to the similar environmental pathogens. On the other hand, outcomes among individuals who do not vary in terms of the susceptibility allele may be determined as a function of variability in environmental exposure. In other words, G × E effects index a genetically determined liability to specific environmental influences. One example

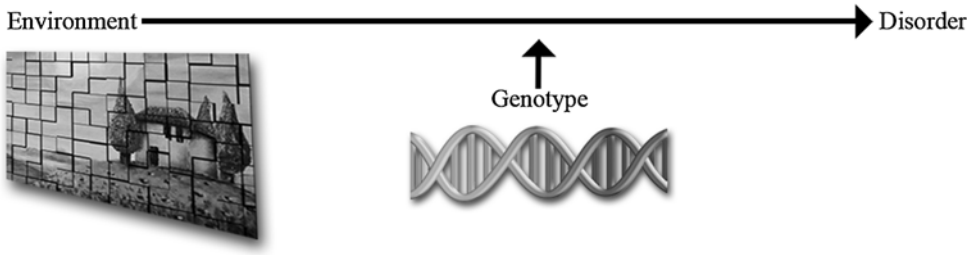

Fig. 1 Environmental factors only lead to a disorder in presence of a specific genetic make-up

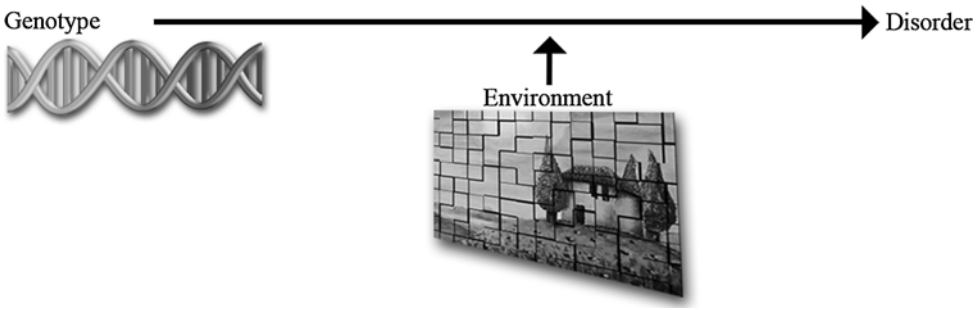

Fig. 2 An individual with a susceptible genetic make-up will only develop a disorder if there are additional environmental pathogens

with one dichotomous genotype (present or absent) of a causative genetic mutation and one dichotomous environmental exposure (exposure vs. non-exposure) is phenylketonuria (PKU) [46]. The development of PKU needs both homozygote mutations in the causative gene encoding phenylalanine hydroxylase, and exposure to phenylalanine [53]. An example for a complex genetic disorder is the alcohol flush reaction after alcohol ingestion in individuals with a genetic variant leading to lowered activity of the aldehyde dehydrogenase (ALDH), a variant which is mainly observed in the Asian population [102]. Carriers of this variant also can develop alcohol dependence after exposure to alcohol, but they are at a much lower risk to do so as compared to those who do not carry this variant. G × E processes will necessarily be more complex if several gene variants and types of environmental exposure contribute to susceptibility for a disease [46], as is almost certainly the case for mental disorders.

The frequent failures to replicate initial genetic findings of association between genotypes and disease might be, among other factors (such as differences in gender ratio, ethnicity, age or comorbid conditions), caused by ignoring simple differences with respect to exposure to relevant environmental factors. If, for example, association has been found in a sample with frequently exposed subjects but not in those infrequently exposed, and exposure has not ascertained, the source of non-replication will remain elusive [69]. G × E studies thus might shed light into the genetically mediated effects underlying both resilience and vulnerability. This might help us to understand and resolve the inconsistency in results found in classical association studies with regard to correlations between disorders and genotypes. G × E findings may also provide helpful insights into the causal processes in pathogen to disorder pathways and therefore shed light on the underlying mechanism of "how an environmental factor external to the person gets under the skin" to result in a mental disorder [69]. As these pathways will vary between disorders, genes have the potential to offer valuable clues to these disorder-specific causal mechanisms [69]. Understanding G × E mechanisms may also provide useful hints with regard to prevention of, and intervention for, mental disorders. New findings in G × E may advance the development of individual therapeutic strategies and lead to pharmacogenetic-based therapeutic innovation [91, 94]. Moffitt et al. [69], along with others, emphasize the importance of G × E and highlight the relevance of strategic gene–environment research.

Limitations and pitfalls in studying G × E

Despite the self-evident value of the G × E strategy there are several methodological challenges. There is the possibility of overestimating effects and false positive findings because of multiple testing and/or data dredging. Along with difficulties in statistical power [16, 63, 107], the susceptibility to artifacts in G × E research has to be kept in mind. Statistically significant interactions are sensitive to alterations in the definition and scaling of the variables being examined: artefactual interactions can be produced by altering scaling [68]. Another problem is how to disentangle G × E from gene–environment correlations (rGE), defined as the probability of a subject's exposure to an environmental pathogen resulting in the association of measures of environmental exposure with genetic variation [19, 87]. G × E may be affected by co-occurring rGE, in which, according to Plomin et al., one can differentiate between passive, active, and evocative rGE [76]. Passive rGE occur because the parents pass on their genes and provide their rearing experiences which may be genetically influenced, e.g., parental qualities [89]. Active-evocative rGE arise because their behavior makes people select their environments and influences other peoples' responses to them [89]. Rutter and Silberg [88] viewed both, G × E and rGE, as different forms of gene–environment interplay. Furthermore, one needs to bear in mind the role of epigenetic effects of environmental influences on gene expression or chromosomal structure and from variations in heritability according to environmental circumstances [68, 83, 87]. For more details on methodological challenges and statistical pitfalls see [28, 30, 37, 46–48, 64, 70, 80, 81, 85, 108]. In order to address these and other problems Moffit et al. [68, 69] defined seven strategic steps for research into measured G × E (see Table 1). More detailed information pertaining to the strategies for careful deliberate G × E hypothesis testing is summarized in [19, 68, 69, 85].

G × E findings for selected mental disorders with onset in childhood and adolescence

Initial indications—seminal studies by Caspi and Moffitt

The first molecular genetic evidence for G × E in child and adolescent psychiatric conditions comes from two classic studies by the research group of Caspi and Moffit [18, 21]. These dealt with conduct disorder, depression and emotional problems. The first study included 442 male participants and demonstrated that the effect of childhood maltreatment was moderated by a functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (*MAOA*) [18]. Carriers of the low-activity *MAOA* genotype who were severely maltreated more often developed conduct disorder, antisocial personality and adult violent crime than

Table 1 Seven strategic steps for research into measured gene–environment interaction (Table adapted from [69])

Step 1: Consulting quantitative behavioral genetic models of the disorder
Step 2: Identifying a candidate environmental pathogen for the disorder
Considerations for selecting environmental risks for inclusion in G × E research on mental disorders
Disorder develops more frequently in persons exposed to the environmental pathogen compared to those not exposed
Variability in response among people exposed to the same environmental risk
Plausible effect of the environmental risk on biological systems involved in the disorder
Evidence that the putative risk is a true environmental pathogen having causal effects
Step 3: Optimizing measurement of environmental risk
Considerations for improved environmental measurement to support G × E research
Proximal measures of environmental pathogens
Age-specific environmental pathogens
The cumulative nature of environmental influences
Retrospective measures of environmental pathogens
Step 4: Systematic genome-wide approach or identifying candidate susceptible genes
Considerations for choosing among candidate genes as they emerge
Common polymorphic variants
Evidence of direct gene-to-disorder association
Functional significance in relation to reactivity to the environmental pathogen
Step 5: Testing for an interaction
Statistical models
Study sampling designs.
Ascertaining the validity of a G × E finding
Step 6: Evaluating whether a G × E interaction extends beyond the initially hypothesized triad of genes, environmental pathogen, and disorder
Step 7: Confirmation in independent samples
Meta-analyses
Validation of findings in G × E studies in experimental studies
Animal models (for example [8])
Functional brain imaging studies (for example [43])
Pharmacogenetics (for example [91, 94])

children with a high-activity *MAOA* genotype [18]. Several researchers carried out studies to replicate this interaction [38, 42, 54, 74, 112]. Despite a number of non-replications a meta-analysis revealed an overall significant effect [54].

The second key study by this group examined G × E in the pathogenesis of depression [21]. In this prospective-longitudinal study the functional polymorphism 5-HTTLPR in the promoter region of the serotonin transporter gene (*SLC6A4*) was found to moderate the influence of stressful experiences occurring over a 5-year period before onset of depression [21]. The carriers of one or two copies of the low expressing short allele of the 5-HTTLPR exhibited more depressive symptoms, diagnosable depression, and suicidality following stressful life events than individuals homozygous for the long allele [21]. Additionally, Caspi et al. [21] detected an interaction between 5-HTTLPR and childhood maltreatment over the period between ages 3 to 11 years. This interaction showed that childhood maltreatment predicted adult depression only among individuals carrying a short allele of the 5-HTTLPR but not among individuals homozygous for the long allele [21].

Depressive disorders

Following the striking initial findings of Caspi et al. [21] studies have replicated the 5-HTTLPR G × E in depression (reviewed in [108]). There have also been a number of failures to replicate [108]. A recent meta-analysis by Munafo et al., however, concluded that the effects of 5-HTTPLR × serious life events (SLE) on risk of depression are compatible with chance findings [70], and a very recent meta-analysis by Risch et al. including published data from 14 studies [22–24, 33, 39, 41, 55, 59, 65, 66, 77, 101, 103, 111] yielded no evidence for an association of the 5-HTTLPR genotype alone or in interaction with stressful life events with an elevated risk of depression [80]. In addition, a gender-specific meta-analysis revealed no sex dependent interaction effects [80]. The failure of these meta-analyses to confirm the initial results of Caspi et al.

[21] may indicate that there actually is no association. Alternatively, sample differences in background genetic and environmental factors could underlie the discrepant findings [80] (see limitations). They could also be explained by the limited comparability of replication studies due to their highly divergent samples, study designs, measures and analyses [80]. Thus, this inconsistency might be caused by methodological differences in the way of evaluating the presence of SLE and in different diagnostic instruments applied in depression (structured face-to-face interviews, questionnaires or telephone/lay interviews, respectively) [29].

Further genes have been investigated with regard to G × E and depression. In their case-only design, Drachmann Bukh et al. [29] detected an interaction between SLE and the genotypes of 5-HTTLPR and BDNF Val66Met on first episode depression. Additionally, they found no 3-way interaction between SLE, 5-HTTLPR and BDNF Val66-Met and no evidence for interactions between SLE and polymorphisms in COMT, TPH1, ACE, 5-HTR2A, and 5-HTR2A, respectively, on depression. According to the authors these results add evidence to the opinion that genes influence the liability to depression not only by main effects on risk but also by control of sensitivity to the pathogenic effects of the environment [29]. This is plausible as variation in the 5-HTTLPR polymorphisms may modulate the serotonergic response to stress [108]. Further evidence for this hypothesis also comes from fMRI studies which show that carriers of the short allele of 5-HTTLPR polymorphism demonstrate amygdala hyperactivity (meta-analysis see [70]) leading to increased cortisol release [32]. There is also an initial indication that SLE and 5-HTTLPR polymorphism interact to predict endocrine stress reactivity in a non-clinical sample [2]. Adults homozygous for the short allele with a significant history of SLE exhibited markedly elevated cortisol secretions in response to the stressor as compared to all other groups, indicating a significant G × E on endocrine stress reactivity [2]. The authors argue that a potential moderating role of HPA axis hyper-reactivity is a premorbid risk factor that increases the vulnerability for depression in subjects with low serotonin transporter efficiency and a history of severe life events.

In the light of the conflicting G × E results with regard to depression, very carefully designed study approaches for testing of G × E hypothesis are urgently required (see "Limitations and pitfalls in studying G × E"; Table 1). Brown and Harris [17] recently outlined inconsistencies with regard to the inclusion of different kinds of environmental factors and the use of a life-course perspective, respectively which may explain the failure of replication of the initial study of Caspi et al. [21]. Brown and Harris hypothesized that in the context of childhood maltreatment the 5-HTTLPR polymorphism contributes to G × E via a direct link with the perpetuation of an adult onset of depression [17]. This is consistent with the hypothesis of early changes in brain function associated with the polymorphism in the context of childhood maltreatment [17].

Attention-deficit/hyperactivity disorder (ADHD)

Molecular genetic research on ADHD has produced a number of plausible candidate genes (e.g., Dopamine D4 receptor gene (*DRD4*), Dopamine D5 receptor gene (*DRD5*), Dopamine transporter (*DAT1*) gene and Catechol *o*-methyltransferase gene (*COMT*)]. However, effects of gene variants identified through association studies are small [34], and the association findings with some markers are inconsistent across different studies (i.e., *DAT1*; reviewed in Banaschweski et al., this issue [6]; [26]). This inconsistency may be due to the moderation of genetic effects by environmental factors that differ between samples. Thapar et al. [105] emphasized that phenotypic complexity, as well as differences in the continuity and changes in clinical presentation over ADHD will both be influenced by the interplay between pre- and perinatal as well as psychosocial, environmental and genetic risk factors. The impacts of environmental factors, such as intrauterine exposure to different drugs (prenatal smoke exposure [9, 49, 57, 71], alcohol consumption during pregnancy [15, 57]), psychosocial adversity [58], mothers' expressed emotion (EE) [15, 78, 95, 96], severe early deprivation [97, 99, 100], or low birth weight [57, 106], have been studied in G × E investigations. Besides highlighting the role of the environment in modulating genetic effects some of these studies provide evidence for a genetic contribution to continuity of the disorder [31, 56, 92] and the development of comorbid anti-social behavior [57, 104, 106].

Prenatal environmental exposures

A prospective study including 161 children suggested that maternal prenatal smoking modifies the impact of the high-risk 10-repeat (10r) *DAT1* allele of the 40-bp VNTR (40 base-pair variable number of tandem repeats) polymorphism in the 3′UTR of the *DAT1* gene [49]. Symptoms of hyperactivity, impulsivity as well as oppositional behavior were increased among children who were homozygous for the *DAT1* 10r allele, but only if those children were exposed to prenatal maternal smoking [49]. However, Neuman et al. [71] failed to replicate this G × E between prenatal smoking exposure and the *DAT1* 10-repeat allele in children with a diagnosis of ADHD, although the odds for a DSM IV-diagnosis of ADHD was 1.8 times greater in children whose genotype at the *DAT1* 3′VNTR contained the 9-repeat (9r) allele and whose mother smoked during

pregnancy than for twins who had neither of these risk factors [71]. Apart from the possibility that the sample was too small this failure to replicate may be due to defining tobacco use in pregnancy as smoking more than 20 cigarettes a day. In a longitudinal study (Mannheim Study of Children at Risk) including 305 adolescents at age 15 years, Becker et al. [9] partly confirmed the findings of Kahn et al. [49], indicating that male homozygous *DAT1*-10r allele carriers with prenatal smoke exposure had significantly higher symptoms of hyperactivity–impulsivity than males from all other groups [9]. In contrast, Brookes et al. failed to confirm the findings of Kahn et al. [49] in a clinical sample [15, 57]. However, this group found evidence for an interaction of a *DAT1* risk haplotype and maternal use of alcohol during pregnancy [15]. Langley et al. [57] failed to replicate this finding perhaps because they did not genotype both markers of the two marker haplotype of *DAT1*. On the whole, the reported inconsistencies in studies of G × E (e.g., for ADHD) elucidate the urgent needs of replication studies with both accurate and consistent measures of environmental factors and genetic variants, respectively, and in meta-analyses [57].

Postnatal psychosocial adversity

The Mannheim Study of Risk Children also showed that carriers of the *DAT1* haplotype comprising the 6-repeat and 10-repeat alleles who grew up in greater psychosocial adversity exhibited significantly more inattention and higher hyperactivity–impulsivity than those with other genotypes/haplotypes or those living in less adverse family conditions [58]. Two recent papers provide more evidence for the potential role of the psychosocial environment in moderating genetic effects in ADHD. Building on previous work highlighting the role of mothers' expressed emotion (EE) as a risk factor for poor outcomes in ADHD [78], the first study [96] examined whether the effects of mothers' EE on ADHD children, in terms of the development of conduct and emotional problems, was moderated by genetic variants in a large sub-sample of the IMAGE study [15]. The results suggested that the impact of EE was moderated by the presence of specific *DAT1* and *5HTTLPR* genotypes; children who did not have the *DAT1* 10r/10r or the 5HTTLPR l/l genotypes showed an effect of EE on conduct problems. As far as emotional problems were concerned, EE had effects only on those who carried the *DAT1* 9r/9r alleles. The second study [99] was carried out as part of the English and Romanian Adoptees (ERA) longitudinal study [86] of the effects of severe early deprivation on development. Previous studies highlighted a link between institutional deprivation and symptoms of ADHD [97, 100], but only in a sub-sample of cases. The results showed that the risk for symptoms of ADHD associated with early institutional deprivation was moderated by the *DAT1* but not the *DRD4* genotypes, an effect that was first apparent in early, and persisted through mid-adolescence. In both studies it appeared that the genetic make-up altered susceptibility of children to variations in their social environment [10].

So far, most G × E studies have employed a candidate gene approach. Studying environmental effects might also be a good strategy for finding potential new genetic markers using purely quantitative strategies such as QTL mapping and genome wide association studies. In the first study of this sort in ADHD, Sonuga-Barke et al. [95] conducted a G × E analysis in the context of a genome-wide association (GWA) scan of the IMAGE study (with 429,981 SNPS available) to identify novel genes whose effects are moderated by high maternal EE. While no G × E effect reached genome-wide significance, a number of nominal significant effects were observed ($P < 0.10^5$) in particular interactions for the genes *SLC1A1* and *NRG3* represent reasonable candidates for further investigation given their previous association with several psychiatric illnesses.

Obesity

Obesity is a multi-factorial trait that results from a complex interplay between genes and environment [62]. The surge in the prevalence of obesity occurred within a short period of time suggesting that environmental and behavioral lifestyle factors play a strong role [1]. G × E is gaining increased emphasis due to the large individual differences in responses to the obesogenic environment—individuals with a genetic predisposition to develop obesity will show the greatest weight gain, whereas individuals with genetic "resistance" to obesity will gain little, if any, weight [1]. Environmental factors influence behavior or lifestyles that determine energy intake or energy expenditure [13]. The differences in individual responses to prevention and treatment strategies, including negative energy balance due to increased energy expenditure and decreased energy intake, seem also to be influenced by individuals' genetic background [14].

There have already been numerous efforts to incorporate genetic and/or gene–environment information into obesity intervention and prevention [14]. Some genes have been reported to be associated with weight loss following intervention (e.g., lifestyle change, pharmacological/dietary interventions, and exercise) (summary [14]). For instance, one polymorphism (rs9939609) in the fat mass and obesity associated gene (*FTO*) was found to have an effect on the body mass index (BMI), which was replicated in other large samples [62]. Individuals homozygous for the risk A-allele weigh on average about 3–4 kg more and

have a 1.6-fold increased risk of obesity as compared to those who have not inherited a risk allele [62]. Furthermore, there is evidence for a significant *FTO* genotype × physical activity interaction, where the physically inactive homozygous carriers of the risk A-allele had an increase in BMI as compared to homozygous carriers of the T-allele [5]. Additionally, other *FTO* variants showed a significant association with physical activity [79]. However, regarding these G × E with *FTO* variants and physical activity the findings in different studies are inconsistent. This could be explained among others by the use of different measurements of physical activity (review [4]).

Additionally, animal models provide evidence for interaction of genetic background and the impact of perinatal and early childhood environments on metabolic, physiological and neuroendocrine functions and their influence on the development of obesity [61]. Furthermore, the systematic GWA study approach holds impressive prospects for the future, provided that the lifestyle factors dietary intake and physical activity are measured accurately because erroneous self-reporting of these factors is a well-known problem (review [4]).

Schizophrenia

The molecular genetic basis of schizophrenia has been extensively studied. The SzGene database ([3]; http://www.szgene.org/) provides an up-to-date ranking list of all relevant *candidate gene variants* (to date in about 30 genes) based on meta-analyses of association studies. Although, as with most complex phenotypes, it is very likely that there may be many rare variants which contribute substantially to the disorder, effect sizes of common single variants are usually small, i.e., average summary odds ratio rarely exceed 1.2 [3]. Evidence for an association between *environmental exposure* and schizophrenia is most solid for paternal age, migration, obstetric complications (fetal hypoxia and proxies for folate deficiency, maternal infection, or stress during pregnancy), urbanicity, and cannabis use, the latter two particularly in case of exposure during development (see [44, 109] for review). Findings from twin, adoption, and family studies generally suggest that a synergy between genetic and environmental factors determines psychotic symptoms and disorder, particularly for exposure to migration, urbanicity, obstetric complications, cannabis, stress, and developmental trauma [109] providing a broad range of potential environmental factors for G × E studies. Generally, the neurobiological mechanism driving the effects of these environmental exposures is unclear rendering the selection of potentially relevant genetic variants for G × E studies difficult.

A few promising hypotheses do exist and some have been tested: a recent study [72] provided initial evidence that variants in four out of 13 tested candidate genes (*AKT1*, *BDNF*, *DTNBP1* and *GRM3*), known to be regulated by hypoxia or involved in vascular functioning in the brain, showed nominally significant interaction with at least one serious obstetric complication event (as a proxy of fetal hypoxia) in 116 patient-trios. Another interesting hypothesis related to obstetric complication is the potential G × E interaction between prenatal virus exposure and genes involved in the immune response, e.g., genes located in the major histocompatibility complex (MHC) region [67]. A first study examining interaction of season of birth and risk variants in the MHC region, however, did not provide any evidence for G × E [98]. Yet, it is possible that prenatal environmental factors may also alter functioning and structure of relevant genes: e.g., folate, which is deficient prenatally in some individuals with schizophrenia, is necessary for normal DNA-methylation and this complicates the picture substantially. Thus, epigenetic changes during neurodevelopment have to be considered.

In the study of Caspi et al. [20], the *COMT Val158Met Val* allele moderated the risk of developing schizophreniform disorder at age 26 following cannabis use in adolescence. Further, in a double-blind randomized controlled trial [45] the *COMT Val* allele was associated with an increased sensitivity to the negative cognitive effects of cannabis in patients with psychoses. In another study [110], the *COMT Met* allele increased the effect of stress on psychotic and affective experiences in daily life in 31 patients with psychosis and cannabis use, but not in non-psychotic cannabis users. There is evidence, derived from animal models (review [44]), suggesting that there are other promising genes (i.e., *neuregulin 1* and the genes regulating the dopaminergic and the GABA system) which potentially moderate the effect of cannabis on the risk of schizophrenia. Furthermore, variation in *Neuregulin 1* was also reported to moderate the effect of high expressed emotion on the level of unusual thoughts in 200 patients with schizophrenia [52].

In conclusion, relatively few G × E interaction studies in schizophrenia are published to date. Promising testable hypotheses based on epidemiological and experimental neurobiological findings are available and need to be examined.

Substance use disorders

Substance use disorders (SUD) are common, multi-factorial disorders, which constitute the leading cause of a wide variety of morbidity and mortality conditions. Both genetic and environmental factors have been implicated in their development, with heritability estimates ranging from 50 to 60% [40]. Moreover, growing evidence suggests that vulnerability to SUD may result from G × E [108]. Among

the brain systems involved in the physiological response to drugs of abuse, much attention has been placed on the hypothalamic-pituitary-adrenocortical (HPA) axis. The link between stressful experiences and substance use has long been discussed [93], with the stress-coping model of addiction proposing that substance use serves to regulate stress-related negative affect. A critical role in the regulation of the HPA axis pertains to the corticotropin-releasing hormone (CRH) system, making the genes encoding the CRH receptors (*CRHR1*, *CRHR2*) prominent candidates for G × E studies. Blomeyer et al. [12] provided the first evidence that genetic variation in *CRHR1* moderated the impact of stress on heavy drinking in adolescents. In 15-year olds, the number of stressful life events during the past 3 years was found to be significantly related to increasing rates of heavy drinking only among individuals homozygous for the C allele of the haplotype-tagging SNP rs1876831. Recently, Schmid et al. [90] demonstrated that the *CRHR1* gene and stressful life events interacted to predict both drinking initiation in adolescence and progression of heavy alcohol use into young adulthood. Findings from animal research support a role for G × E in the development of excessive alcohol intake. In studies with nonhuman primates, Barr et al. [7] revealed that the effects of early stress on alcohol use in later life were conditional on variation in the serotonin transporter gene, with higher consumption only in carriers of the S allele of *5-HTTLPR*. Subsequent studies in humans yielded inconsistent results. While Covault et al. [27] and Kaufman and co-workers [50] found earlier and heavier alcohol use only among carriers of the S allele following stressful life events, Olsson et al. [75] observed a decrease in binge drinking in risk settings with each additional copy of the S allele. Nilsson et al. [73] reported that adolescents with poor family relations had an increased risk of alcohol intoxication when carrying the heterozygous LS genotype of *5-HTTLPR*. Laucht et al. [60] demonstrated that, when exposed to high psychosocial adversity, individuals with the LL genotype exhibited more hazardous drinking.

There are several potential reasons for these conflicting findings. One major reason relates to the fact that substance use and SUD represent a heterogeneous phenotype, which may be differentiated into several subgroups (e.g., Cloninger's typology of problem drinking [25]). However, previous studies usually neglected issues of substance use typology. An additional factor that could have contributed to inconsistency may be the heterogeneity wide variety of in measures of environmental adversity used in the different studies. While in several studies (e.g., [27]) environmental adversity was characterized by exposure to discrete acute events, others focused on chronic difficulties surveyed over a period of years ([73]). However, research on individual differences in biological reactivity to environmental stress has highlighted the duration of a stressor as an important determinant of the stress response.

Conclusions and implications

There is an emerging consensus that interindividual variability in an individuals response to environmental exposures can be explained by genetic moderation of such effects. This gene–environment interplay may explain the individuals' vulnerability and resilience to environmental hazards in the development and expression of mental disorders. In this paper, we have reviewed the current state of the field with regard to G × E in a range of disorders with childhood and adolescent onset. We highlight the progress made to date—some candidate G × E processes have been identified for each disorder and in some cases these have been replicated. Nevertheless, these initial G × E findings have to be interpreted with caution. The replication of G × E findings has in general proved to be challenging—as is also the case for replication of association findings in classical candidate genetic studies. Furthermore, the variance explained by both genetic main effects and G × E effects is invariably small. Initial G × E findings have been challenged by studies using more stringent research designs which better ensure that relations with the measured environmental variables are not influenced by other correlated environmental variables or background common genetic influences [36]. Furthermore, most G × E studies have had only small samples which may explain why G × E effects are difficult to detect and replicate [36]. Besides possible G × E in the pathogenesis of mental disorders, genetic and environmental effects on the course of a disorder during development are important to consider. Even where G × E does not contribute to the initial development of the disorder, it may have a modifying effect on the developmental course and outcome [104]. However, up to now in genetic studies not much attention was paid to the developmental course of a disorder. This is especially true for G × E × Age. Thus, future studies in mental disorders should put more emphasis on G × E in the course of development (see [99]).

Despite all of these caveats and limitations the study of G × E effects—although still in its infancy—offers a number of exciting possibilities across a range of different domains. It will surely stimulate progress in our understanding of the basic neuroscience on childhood onset psychiatric problems. In future genetic research, G × E studies may provide new insights into biological pathways underlying the pathophysiology of mental disorders. It will also play a crucial role in our growing comprehension/investigation of vulnerability [11] and resilience [35, 84]. Longitudinal G × E research will be especially important

as it can help us to better understand heterogeneity in mental disorders. This in turn can be exploited in both the development of new therapies and the targeting of existing therapies. If we can overcome the methodological challenges that face G × E research, the new insights in biological pathways derived from the investigation of G × E might provide new ways of individualized prevention and therapeutic strategies.

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